Arsenic and Arsenic Compounds

CAS Registry Numbers: Arsenic, As, 7440-38-2; Arsenious acid, As_2O_3, 1327-53-3; Arsenic oxide, As_2O_5, 1303-28-2; Arsenic acid disodium salt, Na_2HAsO_4, 7778-43-0; Arsenious chloride, $AsCl_3$, 7784-34-1

As

I. Physical and Chemical Properties

Description	As: Yellow, black or gray solid As_2O_3: White solid
Molecular formula	Arsenic As; Arsenious acid, As_2O_3; Arsenic oxide, As_2O_5; Arsenic acid disodium salt, Na_2HasO_4; Arsenious chloride, $AsCl_3$
Molecular weight	As, 74.92; As_2O_3, 197.82; As_2O_5, 229.82; Na_2HAsO_4, 185.91; $AsCl_3$, 181.28
Air concentration conversion	Not applicable for most compounds; $AsCl_3$: 1 ppm = 7.41 mg/m^3

II. Overview

There is some indication of differential effects of exposure to arsenic in human studies on birth weight and congenital malformations (Nordstrom et al., 1978, 1979ab; Beckman and Nordstrom, 1982) and on neurological development (IQ) (Siripitayakunkit et al.1999; Calderon et al., 2001). Studies in Chile comparing communities exposed to high or low arsenic in their drinking water have indicated an association arsenic exposure with elevated risks of fetal, neonatal, and postneonatal mortality (Hopenhayn-Rich et al., 2000).

Arsenic is a known human carcinogen by inhalation and oral routes of exposure. The principal sites of cancer formation are skin, lung and urinary bladder. Lesser sites include liver and kidney (IARC, 1987; NRC, 1999). The data of Smith et al. (1998) indicate that childhood exposures to arsenic in drinking water may be associated with a significant increase in lung cancer in younger men aged 30-39 years.

Arsenic is teratogenic in mice, rats, hamsters, rabbits, and chicks. Arsenite (As III) has been shown to cause reproductive and developmental effects at significantly lower doses than arsenate (As V). The

effects observed include increased fetal death, decreased fetal weight, and congenital anomalies. The anomalies most frequently reported include neural tube defects, eye defects, renal and gonadal agenesis, and skeletal malformations. Most studies have involved single high doses by gavage or injection. Maternal toxicity was often but not always observed in these studies (OEHHA, 1999a, 2000).

Calderon *et al*. (2001) studied two populations of six to nine year old children exposed to lead and higher or lower levels of arsenic in their drinking water. They concluded that increased arsenic exposure, as indicated by µg urinary arsenic excreted/g creatinine, was associated with an independent decrease in verbal IQ and long-term memory.

Concern for potential differential toxicity of arsenic compounds in children vs. adults is predicated on the carcinogenicity and developmental toxicity of arsenic compounds. The potential neurotoxicity of arsenic in children, possibly in combination with other environmental agents, is also a concern. Studies in mice (Meija et al., 1997) indicate combined effects of lead and arsenic on the central nervous system that were not observed with either metal alone.

III. Principal Sources of Exposure

Arsenic is ubiquitous and is found in low concentrations in soil and water and also in foods, particularly seafood. Ore refining processes, including the smelting of copper and lead, are the major sources by which arsenic dust and inorganic arsenic compounds are released. Arsenic trioxide (As_2O_3) is the most commonly produced form of arsenic. As_2O_3 is used as a raw material for the production of other inorganic arsenic compounds, alloys, and organic arsenic compounds. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 11,303 pounds of arsenic (CARB, 2000). The ambient air concentration in California in 1997 was 1.14 ng/m^3 (CARB, 1999). Concentrations of inorganic arsenic in drinking water can vary significantly. A 1995 survey (ACWA, 1995) covering 180 water agencies in California from 27 counties found the median value of 1500 samples to be 0.002 mg As/L (2 ppb). U.S. EPA (2001) concluded that 20-50 percent of public water systems in the western U.S. had arsenic levels greater than 5 ppb. Thus intake of arsenic from drinking water for an adult consuming 2L/day could be about 10 µg/d. Intake from food sources has been estimated at 50 µg As/d (adults, U.S.EPA, 1988). Thus the airborne contribution to total As intake from ambient air is probably very low (e.g.,1.14 ng/m^3 x 20 m^3/d = 23 ng/d; 0.023 x 100/60.023 = 0.4%).

IV. Potential for Differential Effects

A. Summary of Key Human Studies

A number of investigations were conducted in association with smelting operations in Ronnskar, Sweden and its impact on employees and the population in surrounding areas. The smelter produces copper and lead and a series of other products including gold, silver, zinc, arsenic trioxide, arsenic metal, selenium, nickel sulfate, and red lead. Emissions into the air and water of sulfur dioxide and heavy metals, notably lead, cadmium, mercury, and arsenic, have been studied in a series of investigations. Ronnskar arsenic emissions to air were reported to be 50 tons/year. Emissions of lead, cadmium, and mercury were 200, 5, and 1 ton/year, respectively (Beckman, 1978). Adverse effects on birth weight and increased incidence of congenital malformations were reported; however, arsenic exposures in the area were not well characterized and were confounded by other chemicals, particularly lead and cadmium (Nordstrom *et al*., 1978; 1979a,b; Beckman and Nordstrom, 1982).

The first publication examined the relationship of birth weight in infants of women working at the smelter between 1975 and 1976 and in four areas at varying distances from it (Nordstrom et al., 1978). The latter group consisted of 3688 pregnancies with 2700 single births from a separate region that served as a control (Umea). The average birth weight in offspring of the smelter employees (3391 g) was significantly lower than in Umea (3460 g, $p < 0.05$) and in the two regions farthest from the smelter (C and D; 3495 g and 3470 g, $p < 0.01$, $p < 0.05$, respectively). In the areas (A and B) closest to the smelter (< 10 km), birth weights were also significantly lower (3395 g and 3411 g) than the control ($p < 0.001$ and $p < 0.05$, respectively) and regions C and D ($p < 0.01$-0.05).

Nordstrom et al. (1979a) reports the results of a follow-up investigation of birth weights and birth order among female smelter employees at any time since it began operation in the early 1930s. Birth weight was examined in 881 employees born between 1930 through 1959 and in 2700 controls (Umea). The average birth weight of infants born to employees of the smelter was significantly lower than controls ($p < 0.01$). The decrease was mainly due to pregnancy orders greater than two ($p < 0.001$) and was most pronounced when the mother was employed during her pregnancy. Birth weight normally increases with birth order (as seen in the controls) so the authors note that this was an unusual and significant finding.

Nordstrom et al. (1979b) studied the frequency of congenital malformations in live born children registered at a hospital in the region close to the Ronnskar smelter (Skelleftea) during the period 1955 to 1976 and in children of female employees of the smelter. A total of 694 out of 24,018 live born children (2.9%) were found to have congenital malformations. There was no regional difference in rate or group of malformations in the areas served by the hospital. A temporal difference was observed: 1955-1966, 2.6%; 1966-1976, 3.3%, $p < 0.001$. A total of 39 of 1291 children of employees had malformations (3%). When the mother had worked at the smelter during pregnancy, 17 of 291 had malformations (5.8%) versus 22/1000 (2.2%) if the mother did not work. The difference between these two groups of children was statistically significant ($p< 0.005$). Six children had multiple malformations, and five of these had mothers who had worked at the smelter during pregnancy. For the

five children, the multiple malformations included cleft palate, malformed urethras, spina bifida, multiple bone malformations and multiple digestive and circulatory malformations.

Beckman and Nordstrom (1982) studied rates of congenital malformations and fetal death among wives of 764 smelter workers at the Ronnskar smelter. The reference group consisted of non exposed pregnancies within the same occupational group. The rate of congenital malformations was found not to be related to occupational exposure, smoking habits, or alcohol consumption. The rate of fetal deaths (spontaneous abortions and stillbirths combined) was significantly increased in pregnancies where the husbands were exposed, after adjustment for parental age and pregnancy order ($0.01<p<0.05$). The results suggest that fetal death is caused by germ cell damage through occupational exposure of fathers.

Calderon *et al*. (2001) conducted a cross-sectional study to examine the effects of chronic exposure to lead (Pb), arsenic (As), and nutrition on the neuropsychological development of children. Two populations of children aged six to nine years (N = 41, 39) with differing As exposure levels (63 v. 40 µg/g) but similar Pb exposures (8.9 v 9.7 µg Pb/dL blood, respectively) were compared using the Wechsler Intelligence Scale for Children (WISC) Revised Version for Mexico. After controlling for significant potential confounders, verbal IQ was observed to decrease with increasing urinary arsenic ($p < 0.01$). Language, verbal comprehension and long-term memory also appeared to be adversely affected by increasing arsenic exposure (concepts and knowledge factors, $p < 0.05$ each). Blood lead was significantly associated with a decrease in attention (sequential factor, $p < 0.05$). However since blood lead is an imprecise measure of lead burden there could be some residual confounding in this study.

The relationship between arsenic exposure via drinking water and neurological development as indicated by intelligence (IQ) was assessed in Thailand (Siripitayakunkit *et al*., 1999) in 529 children aged six to nine years using a cross-sectional design. Arsenic levels in hair were used to assess exposure and the WISC test for children was used to assess IQ. The range of arsenic concentrations in hair was 0.48 to 26.94 µg/g. The mean IQ of the study was 90.44 (range 54 to 123). Most of the IQs were classified as average (45.7%) or dull normal (31.6%). Approximately 14% and 3% of the children were in the borderline and mental defective groups, respectively. The percentage of children in the average IQ group decreased significantly from 57 percent to 40 percent with increasing arsenic exposure. The percentage in the lower IQ group increased with increasing As (23% to 38%) and in the low IQ group (zero to six percent). In a comparison of IQ between children with As hair levels ≤ 2 ppm or > 2 ppm, arsenic was found to explain 14 percent of the variance in IQ after controlling for father's occupation, mother's intelligence score, and family income. Arsenic levels in hair above 2 ppm were associated with a 0.75 point decrease in IQ below the grand mean, and As levels above 5 ppm with a two point decrease. Although the cross-sectional study design does not allow for establishment of the time precedence of exposure to arsenic, the investigators stated that the subjects of the study were born in a period of chronic arsenic poisoning and that this cohort has been continuously exposed since birth due to their non-mobility. The study suffers from small numbers of children exposed to low arsenic (hair arsenic ≤ 1 ppm) so this group could not be compared to the high arsenic children. Also the possible exposure to chemical confounders like lead is not discussed.

Hopenhayn-Rich et al. (2000) conducted a retrospective study of chronic arsenic exposure and risk of infant mortality in two areas of Chile: Antofagasta, with a documented history of As contaminated drinking water and Valparaiso, a comparable low-exposure city. Between 1950 and 1996, Antofagasta experienced an 86 percent decline in the late fetal mortality rate, an 81 percent decline in neonatal mortality rate, and a 92 percent decline in the post neonatal mortality rate. The declines in fetal and infant mortality rates in Valparaiso were 64, 77, and 92 percent, respectively. Despite the overall decline, rates for all outcomes increased in Antofagasta during 1958-1961 and declined thereafter. The increases and declines overall coincide with the period of higher arsenic levels in the drinking water. Results of a Poisson regression analysis of the rates of late fetal, neonatal and postneonatal mortality showed elevated relative risks for high arsenic exposure in association with each of the three mortality outcomes. The association between arsenic exposure and late fetal mortality was the strongest (RR = 1.72; CI, 1.54-1.93). Neonatal mortality (RR = 1.53; CI 1.40-1.66) and postneonatal mortality (RR = 1.26; CI, 1.18-1.34) were also elevated. These findings provide suggestive evidence for arsenic-related human developmental toxicity.

Ihrig et al. (1998) conducted a hospital-based case-control study of stillbirths and environmental arsenic exposure using an atmospheric dispersion model linked to a geographical information system. They collected data on 119 cases and 267 controls in a central Texas area including a facility with 60-year history of arsenic-based agricultural product manufacture. Four exposure groups were categorized (0, < 10 ng/m^3; 10-100 ng/m^3; and > 100 ng/m^3). For the period 1983-93 they fit a conditional logistic regression model including maternal age, race/ethnicity, parity, income group, exposure as a categorical variable, and exposure-race/ethnicity interaction. Effects were only seen in the Hispanic group with the medium exposure group having a prevalence odds ratio and 95% confidence interval of 1.9 (0.5-6.6) and the high exposure group 8.4(1.4-50.1). The authors postulate a possible influence of a genetic polymorphism affecting folate metabolism in Hispanic populations possibly leading to increased neural tube defects and stillbirths. This study is limited by small numbers, for example there were only seven cases in the high exposure group and five of these were Hispanic.

Smith et al (1998) studied lung and urinary bladder cancer mortality in a region of northern Chile (Antofagasta) where the residents were exposed to arsenic in their drinking water. Arsenic levels ranged from a population weighted average of 570 µg/L between 1955 and 1969 to 100 µg/L by 1980. The mortality ratios (observed/expected deaths) for bladder, kidney, liver, and skin cancers, and all other cancers combined, were not related to age in either sex. However, lung cancer mortality ratios were particularly high in younger men aged 30-39 yr (SMR = 11.7, 95 percent CI 6.4-19.6, $p < 0.001$). Also observed was a decreasing trend in chronic obstructive pulmonary disease deaths (COPD), with higher rates among younger men, particularly those aged 30-39. Four COPD deaths were reported among men (0.8 expected), and six deaths among women (0.1 expected). These ten individuals who died of COPD would have been young children at the time of peak arsenic water levels in 1955-1970. Additional evidence supporting a link between childhood arsenic exposure and subsequent lung disease comes from autopsies of children in the affected area. The results of five autopsies of children who died in 1968 and 1969 in Antofagasta showed evidence of arsenic poisoning including skin lesions; lung abnormalities were observed in four of the children whose lungs were examined. Two of these cases exhibited interstitial fibrosis (Rosenberg, 1974). Also, in a survey of

144 children in Antofagasta with skin pigmentation due to arsenic exposure, bronchopulmonary disease was 2.5-fold more frequent than in children with normal skin (15.9 vs. 6.2 percent, respectively) (Borgono et al. 1977).

B. Summary of Key Animal Studies

Nagymajtenyi *et al*. (1985) exposed pregnant CFLP mice (8-11 females/group) to As_2O_3 for 4 hours/day on gestational days 9-12 at concentrations of 0, 0.26, 2.9, or 28.5 mg As_2O_3/m^3 (~0.2, 2.2, and 21.6 mg As/m^3). A statistically significant decrease in fetal weight was observed in all the dose groups ($p < 0.05$), with a 3, 9, and 29% reduction in average fetal weight with increasing dose. Significantly increased fetal malformations were observed only in the highest dose group, primarily delayed ossification, with an apparent positive dose-related trend in the number of fetuses with malformations (3, 7, and 31, respectively). A similar dose-related trend in chromosome aberrations in liver cells was also observed in the number of cells with chromosomal damage: chromatid gaps, chromatid breaks, chromosome fragments, and chromosome breaks. Only the number of damaged cells and chromosome breaks at the high dose were significantly different from the control ($p < 0.05$).

Hood (1998) injected mice with 1200 or 1500 mg/kg-d methanearsonic acid (MMA) or with 800 or 1200 mg/kg-d dimethylarsinic acid (DMA) on gestation days 8 thru 14. MMA and DMA are the primary metabolites of inorganic arsenic in most animals and humans. Both arsenicals induced prenatal mortality and malformations in the developing offspring following maternal treatment on single gestation days. However, the doses employed were extremely high and "in the maternally toxic range".

Studies in mice exposed to sodium arsenite (11 or 13.8 mg/kg-d) and/or lead acetate (116 mg/kg-d) for 14 days have demonstrated both individual and combined effects on the central nervous system. Specifically arsenic was found to decrease norepinephrine levels in the hypothalamus and increase 5-hydroxyindole-3-acetic acid in the midbrain and striatum and to increase dopamine in the striatum. Treatment with lead and arsenic combined gave a 38 percent decrease of norepinephrine in the hippocampus that was not seen with either metal alone (Meija et al., 1997).

V. Additional Information

A. Other Respiratory Toxicity

Wulff *et al*. (1996) studied the risk of cancer in children born to women living in the vicinity of the Ronnskar smelter in Sweden. Thirteen cases of cancer were diagnosed in children born in the vicinity of the smelter compared to 6.7 cases expected based on national rates (Standardized Incidence Ratio (SIR) = 1.95, 95% C.I. 0.88-3.0) although this difference was not statistically significant. The SIR for the reference group was 1.0 (95% C.I. 0.7-1.30). Leukemia was the most common cancer in both

groups. Confounding exposures from other chemicals are still an important qualification as noted above for earlier studies of this site.

Bencko et al. (1977) analyzed hearing changes in a group of 56 10-year-old children residing near a power plant burning local coal of high arsenic content. The control group consisted of 51 children of the same age living outside the polluted area. Thresholds of hearing were examined at frequencies of 125-8000 Hz for air conduction and 125-4000 Hz for bone conduction. Hearing losses for air conduction were found in the exposed group at 125-1000 Hz and at 8000 Hz ($p = 0.0005$-0.05). For bone conduction hearing losses were seen at 125-500 Hz and 4000 Hz ($p = 0.0005$-0.05). Clinical examination showed a higher rate of enlarged tonsils and adenoids and concomitant phlegm-pus flow in the posterior nasopharynx in the exposed group versus the controls. However, history of more frequent nasopharyngeal and middle ear infections was lower in the exposed group compared to controls. The high statistical significance of the hearing impairments observed suggests that auditory damage, including total deafness, may be associated with arsenic exposure in these children. Auditory damage caused by arsenic poisoning has been observed in animal studies and in clinical experience (early German papers cited in Bencko et al., 1977).

B. Regulatory Background

An inhalation chronic REL of 0.03 $\mu g/m^3$ has been established by OEHHA based on reduction in fetal weight and increased incidence of growth retardation and skeletal malformations in mice (OEHHA, 2000). An inhalation acute REL of 0.19 $\mu g/m^3$ was set by OEHHA based on decreased fetal weight in mice (OEHHA, 1999a). Inorganic arsenic compounds are recognized as chemicals known to cause cancer and reproductive toxicity under Proposition 65 (Safe Drinking Water and Toxic Enforcement Act of 1986). The current inhalation cancer potency is 12 $(mg/kg\text{-}d)^{-1}$ or 3.3×10^{-3} $(\mu g/m^3)^{-1}$. The current oral cancer potency is that established by U.S. EPA of 1.5 $(mg/kg\text{-}d)^{-1}$ based on human skin cancer incidence (U.S.EPA, 1988; OEHHA, 1999b).

VI. Conclusions

Although there is evidence that infants and children may be more susceptible to arsenic exposure than adults, airborne exposures are very low and represent a small percentage of total exposure to arsenic. Thus arsenic has been placed in Tier 2. We may reconsider listing arsenic in future updates, particularly if evidence of significant exposures arise.

VII. References

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